DETAILED ACTION

Status of the Application

Claims 17-24 are pending.

Applicant's cancellation of claims 1-3, 6-13, 15-16, addition of claims 17-24, and amendments to the specification as submitted in a communication filed on 1/9/2008 are acknowledged.

The submission of a new sequence listing on 1/9/2008 is acknowledged. However, this sequence listing has not been entered due to errors in the submission. A validation report describing the problems found is being submitted with this Office action. Applicant is requested to submit a compliant sequence listing in response to this Office action.

New claims 17-24 are directed to the subject matter previously examined. Claims 17-24 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The specification remains objected for failing to comply with sequence rules. While Applicant has amended the Brief Description of the Drawings section regarding Figure 9, the sequence identifiers recited are not present in the current sequence listing as filed on 3/15/2004.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 17-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 17 (claims 18-24 dependent thereon) is indefinite in the recitation of "having motifs X, I, II, III, IV, …and VIII such that the first and second DNA segments are joined at a site next to or within motif 1 or motif IV" for the reasons indicated in the Non Final action of 7/20/07 and those set forth below.

First, as written, it is unclear how the chimeric restriction endonuclease can have methylase activity if the claim does not require the chimeric DNA (1) to encode all the nine motifs, or (2) to encode the methylase motifs in the order described by Figure 9. It is noted that as written, the second DNA can encode the specificity domain followed by the C-terminal portion of a gamma methylase domain. Therefore, the chimeric DNA can have a structure encoding a cleavage domain, followed by the N-terminal portion of the first methylase, the specificity domain, and the c-terminal portion of the second methylase. Since the specificity domain would disrupt the chimeric methylase domain, it is unclear as to how this chimeric protein can have methylase activity. Also, since the claim requires (1) the first DNA to encode any N-terminal portion of the gamma methylase, and (2) joining the DNAs at a site next to or within motif I or motif IV, the chimeric endonuclease can lack motifs X, I, II and III. Since it has been suggested that these motifs are required for enzymatic activity, it is unclear if a chimeric enzyme lacking these motifs will have methylase activity.

In addition, as previously indicated, the motifs are indefinite because one cannot determine the structure of these motif (i.e., consensus sequence). Applicant has indicated in the response filed on 1/9/2008 that motifs I and IV are defined by the consensus sequences I/VLD/EPSCGXGXF/LL and F/YDXIIGNPPY, respectively. However, it is noted that neither the consensus sequences provided in the response for motifs I and IV nor the consensus sequences for the remaining motifs have been provided in the specification or in the Malone et al. reference. It should be noted that Applicant has not provided any basis for consensus sequences provided. For example, assuming that the start of motif I is the first amino acid shown in the alignment provided under the heading "Motif I", it is unclear to the examiner what was

the basis for selecting amino acids 1-2, 4-7, 11 and 12 of the consensus provided by Applicant as motif I if the alignment of Malone et al. shows endonucleases having G/L/F at position 1 in addition to I/V, C/I at position 2 in addition to L, A/L/G at position 4 in addition to P, A/G/C/F at position 5 in addition to S, F/A/S at position 6 in addition to C, A at position 7 in addition to G, S/I at position 11 in addition to F/L, and S/T/I/A/R at position 12 in addition to L. Similarly, it is unclear to the examiner what was the basis for selecting the amino acids of positions 1, 2, 4-6 and 10 of the consensus provided by applicant as motif IV when other amino acids are also shown in these positions as set forth in the alignment of Malone et al. While Figure 9 shows the alignments which led to the assertion that gamma methylases have these motifs (Figure 1C of Malone et al.), the actual consensus sequences for these motifs are not provided and in some cases their boundaries are ill-defined (e.g., motif V and VI). For examination purposes, no patentable weight will be given to the motifs recited. Correction is required.

5. Claims 18-19 are indefinite in the recitation of "wherein the first/second DNA is deficient in methylase/DNA cleavage activity" because it is the proteins encoded by these DNAs and not the DNAs recited which have enzymatic activity. For examination purposes, it will be assumed that the claims recited "wherein the first/second DNA encodes a protein deficient in ….activity". Correction is required.

6. Claim 21 (claims 22-23 dependent thereon) is indefinite in the recitation of "(a) ligating the first DNA to the second DNA, wherein the first DNA is formed by restriction endonuclease….; or (b) selecting primers for amplifying the first and second DNA fragments by two-step PCR to form the chimeric type IIG restriction endonuclease" for the following reasons. Claim 17, from which claim 21 depends, requires forming a chimeric DNA by joining two DNAs. The term "ligating the first DNA to the second DNA" does not further limit the claim because "joining" and "ligating" are essentially equivalent terms. In addition, it is unclear as to how the term "(b) selecting primers for amplifying..." further limits a method which requires joining the two DNAs. It is noted that if the intended limitations are limitations regarding how the two DNAs are obtained prior to joining them, the claim should be

amended to recite, for example, "the method of claim 17, wherein (a) the first and second DNAs of (i) and (ii) are obtained by cleavage with a restriction endonuclease, or (b) the first and second DNAs of (i) and (ii) are obtained by PCR amplification". Claim 22 should be amended to recite, for example, "the method of claim 21, wherein a linker is used to join the first and second DNAs of (i) and (ii)". Correction is required.

7. Claim 23 is indefinite in the recitation of "the cleavage site being unique within the DNA encoding the restriction endonuclease" as it is unclear which restriction endonuclease is being referred to. Claim 17, from which claim 23 ultimately depend, refers to three different restriction endonucleases, the restriction endonuclease encoded partially by the first DNA of (i), the restriction endonuclease encoded partially by the second DNA of (ii), and the chimeric restriction endonuclease. For examination purposes, it will be assumed that the term reads "the cleavage site being unique within the chimeric DNA encoding the chimeric restriction endonuclease". Correction is required.

8. Claim 24 is indefinite in the recitation of "chimeric Type I G restriction endonuclease" because there is no antecedent basis for the chimeric Type I G restriction endonuclease. It is suggested the term be amended to recite "Type II G". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 17-24 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the Non Final action mailed on 7/20/2007. It is maintained for the reasons of

record and those set forth below.

11. Applicant traverses the rejection on the grounds that the type IIG family has specific characteristics, namely (1) a cleavage domain, a methylase domain and a specificity domain in a single peptide, (2) cleavage of substrate at an approximately fixed distance outside the DNA recognition sequences, and (iii) a subset of type IIG restriction endonucleases have a gamma type methylase with motifs ordered as shown by Malone et al. (motifs X, I, II, III, IV, V, VI, VII and VIII with the specificity domain after motif VIII.

12. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the instant rejection. The examiner acknowledges the teachings of Roberts et al. (Nucleic Acids Research 31(7):1805-1812, 2003; cited by applicant in the response) regarding type II restriction endonucleases, and those of type IIG restriction endonucleases. However, the examiner disagrees with applicant's contention that the characteristics provided are sufficient for one of skill in the art to envision the structure of any type IIG restriction endonuclease, or its corresponding DNA, as required to practice the claimed method. As indicated previously, neither the specification nor Malone et al. clearly define the consensus sequences for the motifs recited, X, I, II, III, IV, V, VI, VII and VIII. In addition, even if it is assumed that these motifs are defined, neither the specification nor the art provides any information as to the additional structural features required in the cleavage and recognition domains such that one of skill in the art can reasonably conclude that the structural features provided constitute a substantial portion of the entire genus. Therefore, for the reasons set forth above and those of record, one cannot reasonably conclude that the recited genus of nucleic acids is adequately described.

13. Claims 17-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for creating a functionally active chimeric type IIG restriction endonuclease in a transformed host cell by combining the catalytic, methylase, and specificity domains of restriction

endonucleases BpmI, BsgI, ThaIV and AcuI, does not reasonably provide enablement for creating a functionally active chimeric type IIG restriction endonuclease in a transformed host cell by combining any cleavage/methylase/specificity domains of any type IIG restriction endonucleases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in the Non Final action mailed on 7/20/2007. It is maintained for the reasons of record and those set forth below.

14. Applicant traverses the rejection on the grounds that the specification provides working examples and describes how to make several different chimeric type IIG restriction endonucleases. Furthermore, applicant argues that the specification also discloses how to make deletions, the use of linkers of various sizes to enhance the activity of the chimeric enzyme, and the use of an SOS induction assay for rapid screening.

15. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of the instant claims. The examiner acknowledges the teachings of the specification and agrees that working examples, methods for making deletions, the use of linkers and methods for rapid screening have been provided. However, as previously indicated, the enablement provided is not commensurate in scope with the claims due to the extremely large number of DNAs encoding type IIG endonucleases of unknown structure. The method as claimed not only requires those DNAs encoding type IIG endonucleases which are known in the art but it also encompasses DNAs encoding type IIG endonucleases yet to be discovered. As discussed above, the motifs recited for the methylase domain are not well defined. In addition, as indicated above, even if it is assumed that the motifs recited are well defined such that there is a structure/function correlation for the methylases recited, the claims also require the cleavage and specificity domains, for which there is no structure/function correlation disclosed sufficient for one of skill in the art to envision the structure of any complete type IIG endonuclease. As

previously stated, while methods of isolating/generating variants of a nucleic acid were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for any number of nucleic acids and determine which ones encode type IIG restriction endonucleases. In the absence of some knowledge or guidance as to the structural features required in any DNA encoding a type IIG restriction endonuclease such that one could select a limited number of species for testing, one of skill in the art would have to go through the burden of undue experimentation to enable the entire scope of the claims. Thus, one cannot reasonably conclude that the claimed method is fully enabled by the teachings of the specification or those of the prior art.

Conclusion

16. No claim is in condition for allowance.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

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DR
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